

Proceeds from the European workshop:

GBS neonatal disease prevention, Granada 23 November 2002

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Introduction

In many industrialized countries, since the 1980's, Group B streptococcus (GBS) became and remains the most important pathogen causing neonatal invasive infections, reported attack rates ranging from 1.0 to 4.7 per 1,000 live births.¹⁻³ As recently demonstrated, up to 75 % of cases can be prevented by an intrapartum antibioprophylaxis given to selected women at risk of delivering a neonate who will present shortly after birth a severe GBS infection^{4,5}. As recommended by CDC in 1996, these women can be identified either on a prenatal culture-screening based approach or on a risk-based approach.⁶ Based on data available since 1996, the screening approach has been demonstrated more effective than the risk-based approach; therefore, in August 2002, CDC issued revised guidelines which recommend a universal screening based approach for ALL pregnant women.⁷ Other strategies are still investigational as vaccine or vaginal intrapartum disinfection with chlorhexidine.⁸⁻¹² In Europe, epidemiological data regarding GBS neonatal diseases are rather poor and the known or estimated attack rates seem to vary a lot from one country to another. Some countries, as Spain, have already issued guidelines for the prevention of GBS perinatal diseases ; and, from one country to the other, these guidelines, if they exist, can be rather different in their recommendations.

The aim of the Granada GBS workshop was to think about GBS neonatal burden in Europe and to look for useful tracks that European should follow for the prevention of these GBS perinatal diseases.

Workshop (scientific program attached to this document)

For the success of strategies for prevention for GBS perinatal disease, gynecologist-obstetricians, microbiologists, neonatologists and all related health-care providers should work together as a team and should comply with the same recommendations. To have a useful workshop, the organizing committee minded to invite equally either as speaker or as attendee, obstetricians, microbiologists and pediatricians. Nine European countries were represented: Austria, Belgium, France, Germany, Italy, Norway, Portugal, Spain and United Kingdom, with a great majority of Spaniards. Furthermore, four reference North American speakers were also invited: S.Schrag from the CDC in Atlanta, USA, WE.Benitz pediatrician from the Sandford University, USA, D.Davies, also pediatrician, from the University of Calgary, Canada, and P. Della-Latta, microbiologist at the Columbia Presbyterian Medical Center in New York, USA.

To introduce the workshop, S.Salcedo and J.Vinzo (Spain) stated the global GBS neonatal burden, reviewed the different approaches to prevent perinatal GBS infections and opened some questions for further discussion. Than WE.Benitz gave a comparative analysis of GBS prevention strategies and argued benefits, cost-effectiveness and adverse effects observed or to expect with the different strategies. After that we got some analysis of the European situation with data from UK, France, Italy, Austria, Germany and Spain. The lowest

observed attack rate is 0.5 per 1,000 live births in UK and the highest in France with 4.8 cases of early onset disease per 1,000 live births. From this analysis of the European situation, two main problems have emerged : the definition of a case and the method to get or to collect data. Spanish speakers illustrated the impact of their guidelines and their success in reducing strikingly the attack rate of GBS early onset disease, from 2 to 3 per 1,000 in the mid-1990s to less than 0,5 per 1,000 live births in 2002.

In the following session, S.Schrag from the CDC presented the first U.S. consensus recommendations issued by CDC in 1996 (ACOG 1996 and AAP 1997), their impact, benefits and adverse effects observed or to expect, and their re-evaluation in November 2001. She argued the choice made in the revised guidelines issued in 2002, a universal culture-screening based strategy, and stressed things that remain the same and the areas of change. JM Foidart (Belgium), obstetrician, emphasized the importance of systematic attitude, the requirement for good documentation and communication (the right information must be at the right place at the right time), the importance to be creative finding the means to get gynecologists, microbiologists and pediatricians working together as a team and to facilitate compliance to recommendations. M de la Rosa reviewed all the important microbiological characteristics of GBS, methods for detection of GBS, and the improvement and drawbacks to expect from culture on Granada agar. On Granada agar, GBS are very easily detected, they grow as typical orange-red colonies. But the good manufacturing procedures and storage conditions are critical for its quality. As reported by different speakers, rapid PCR detection of GBS could become, rather shortly, a very promising tool in prevention strategy. In this session, P. Della-Latta also presented the current microbiological practices for GBS screening in the US and suggested some improvements to get a higher sensitivity and a shorter turn-around time for GBS prenatal screening cultures. A.Andreu (Spain) confirmed the reduction in the attack rate of GBS neonatal diseases observed in Spain consecutively to implementation of the Spanish guidelines. She also stressed advantages of direct plating and subculturing Lim broth onto Granada medium agar for the prenatal screening.

The third session dealt with neonatal management and special problems. D.Davies, from Canada, reported the successful Canadian experience in reducing incidence of perinatal GBS diseases and debated special problems as incomplete prophylaxis, cesarean delivery and allergies to penicillin. Than WE.Benitz reviewed controversies and uncertainties regarding the management of babies at risk for GBS disease as reflected through CDC's guidelines. He proposed to stratify babies in intermediate and high risk babies and gave suggestions for their management, evaluation and treatment. In summary, he suggested no intervention for well infants without maternal risk factors, diagnostic evaluation and empiric treatment of infants born to women with PPRM or chorioamnionitis, and those with signs of illness, and postpartum prophylaxis or limited diagnostic evaluation for intermediate risk infants (identified by risk criteria). In this session, another very interesting approach for prevention was also reported and could probably be integrated in the future in a new strategy for prevention. B.Stray-Pettersen from Norway, reported a very interesting and impressive reduction of GBS early onset disease obtained with a universal vaginal intrapartum douching with 140 ml of a solution of clorexidine (every 6 hours until delivery) combined with intrapartum antimicrobial prophylaxis for selected high risk .

All these different presentations were opened for discussion and were followed by an interactive session.

For the last session, an interactive session, each participant had received an individual keypad to vote electronically " in real time" on each key point of a strategy they would like to recommend in Europe for the prevention of perinatal GBS diseases. To have an idea of non Spanish European votes, results were gathered in two categories Spaniards (SP) and non Spanish European (EU). To reach a consensus, we fixed an 80 % cut-off of agreement between participants.

Interactive session : summary of the results

Who should issued guidelines to get the highest compliance level ? Before starting with guidelines to recommend in Europe, the attendance was asked to give its opinion regarding the type of guidelines which could get the highest level of compliance. There was no difference between SP and EU participants' opinion: 57% believed that European guidelines would be the best, 15% thought that national guidelines would be better and the others thought that it does not matter if guidelines were European or national. The same question was asked regarding the organization that would issue these guidelines. They could choose between Department of Public Health, one of the related professional and scientific European societies (ESCMID, Obstetrics and gynecology or Pediatrics), and all these three societies together, after a consensus. For EU participants it was clear, 93% thought future guidelines should be launched after a consensus by all three European societies, only 7% would prefer a Department of Public Health. Among SP, 74% agreed with the choice of the three societies, 12 % with the Public Health department and 14% believed in compliance even if guidelines were launched by only one of the three Societies.

"Ideal" strategy to recommend in Europe. Among SP, who already have guidelines recommending selective intrapartum antimicrobial prophylaxis based on a universal screening strategy, 69% would recommend the same, 4% would prefer a risk-based approach, 12.5% would like to have both alternatives and 12.5% would like a new approach combining selective antimicrobial prophylaxis with universal or selective vaginal disinfection. Only 47% of EU were in favor of a universal prenatal screening based strategy, no one would recommend a unique risk-based approach but 27% would prefer to recommend both approaches as in the previous CDC recommendations. As some SP did, 20% of EU would like to propose a new approach combining selective antimicrobial prophylaxis with universal or selective vaginal disinfection. It's interesting that a few SP (2%) or EU (7%) did not want to recommend anything for prevention of GBS diseases.

If a selective intrapartum antimicrobial prophylaxis based on a universal screening strategy should be recommended in Europe, 54% of the EU participants thought, that in their country, it could be achievable within a few months, 38% thought it would not be possible for logistic problems and 8% for financial reasons (national health budget, level of reimbursement for cultures, etc.). For SP, of course it was quite different and 88% thought it would be shortly achievable, however 5% opposed financial problems and 2% logistic problems.

If a clinically proven effective rapid GBS screening test became available, half of the participants either SP or EU would be in favor of their integration into the screening based strategy for an rapid screening at admission of women for delivery. For nearly 40% of EU and 20% of SP, the major obstacle to this issue was that too many hospitals or clinics do not have adequate laboratory facilities 24 hours a day, 7 days a week. Only one EU and 21% of SP did not believe the benefit could balance their drawbacks.

Related to the antimicrobial agent to recommend as first choice, all EU except one would recommend "Penicillin G" at 5 MIU IV initial dose + 2.5 MIU IV every 4 hours until delivery as the most appropriate regimen. Among SP, only 73% agreed with this choice and 24% would recommend another agent. Unfortunately, none of them wanted to comment their opinion. For the alternative to recommend in penicillin-allergic patients, the opinions were more scattered. Only 35% of EU and 29% of SP would recommend Cefazolin for penicillin-allergic patients not at high risk for anaphylaxis, which is the drug currently recommended by CDC guidelines. In fact data relative to clindamycin and erythromycin resistance for GBS in Europe are still very poor, even if some data as from Belgium, showed a trend in emergence of resistance (10-15% in 2002).

Regarding the clinical specimens to collect for the GBS prenatal screening, 80% of EU and 93% of SP would recommend both vaginal and rectal swabs. No EU would recommend a vaginal swab alone but 20% would propose other specimens. For the laboratory procedure for prenatal GBS cultures, many of participants were convinced to use Granada medium agar, either by their own practice for SP or by the different data presented along the meeting: 64% of EU and 87% of SP would recommend either direct plating or subculturing from Lim broth onto Granada medium.

One major problem for pediatricians, related to selective antimicrobial prophylaxis prevention strategy, is the management of asymptomatic newborns exposed to intrapartum prophylaxis. Convinced by Dr Benitz's data and based on their own experience, 67% of EU and 54% of SP would consider a full diagnostic evaluation and giving an empiric antimicrobial therapy at least 48 hours to asymptomatic neonates born to a mother with at least two of the following risk factors: GBS vaginal colonization, < 35 weeks gestation, intrapartum T° ≥ 38° C, prolonged rupture of membranes > 18 hours; furthermore, 28% of EU and 36% of SP would also recommend the same attitude when the mother received antibiotics for a suspected chorio-amnionitis.

As the GBS neonatal epidemiology has been rather dynamic in the last three decades and with guidelines to reduce the GBS neonatal burden implemented in different countries, surveillances to monitor incidence of GBS and non-GBS early onset diseases, to monitor risk factors associated with early onset diseases and the potential adverse effects of chemoprophylaxis, are desirable. Most of SP (88%) and of EU (75%) were ready to participate in a European surveillance project.

Summary and concluding remarks (P. Melin, Belgium and C. McCartney, UK)

- Associated to high morbidity and mortality, infection due to *S.agalactiae* either in newborn infants or their prevention is also a major public health problem in Europe. Some differences exist between different European countries and few of them have already issued guidelines for the prevention of neonatal GBS diseases.
- Epidemiological surveillances and a standardized definition of cases would be highly desirable.
- From the different speakers, clearly the success of recommendations to reduce the GBS burden by preventing early onset neonatal GBS diseases is linked to cooperation between the different partners dealing with health care to pregnant women and with deliveries. Obstetricians, microbiologists, pediatricians and all related health-care providers have to work as a TEAM. They have to organize a good communication of results and observations to the right person, at the right place as soon as available.
- A consensus was reached to wish common guidelines issued by obstetrics, microbiology and infectious diseases and pediatrics European societies.
- Even if a prenatal screening based approach to identify mothers with an indication for antimicrobial prophylaxis was evidently more effective than a risk-based approach, a consensus was not reached within the attendance, but only a majority in favor with the screening approach. For the prenatal screening, a consensus was reached to recommend both vaginal and rectal swabs for the clinical specimens to collect.
- Regarding laboratory procedure for prenatal screening cultures, the Granada medium agar as a selective differential medium for GBS would be recommended by a majority of the participants either as primary culture or for subculturing Lim Broth.
- Interestingly, more than 50% would integrate rapid intrapartum testing for GBS screening when a relevant test would become available.
- Another important learning during this meeting was the demonstration of efficacy of the Norwegian strategy to reduce the attack rate of GBS neonatal disease. This strategy, based on a universal intrapartum vaginal disinfection with chlorhexidine has attracted numerous participants.
- For the antimicrobial agent to recommend for the intrapartum antimicrobial prophylaxis, a consensus was reached for Penicillin G, but opinions were less clear regarding the alternative agent to recommend for penicillin-allergic women.

- For the management of asymptomatic neonates exposed to prophylaxis, a majority of participants would like to consider a full diagnostic evaluation and giving an empiric antimicrobial therapy at least 48 hours to selected high risk neonates.

For the future :

- European are currently too far from each other to propose a consensus for the prevention of neonatal GBS diseases. First, surveillances are needed. ESCMID could play a role in encouraging and funding a European surveillance of GBS and non-GBS early onset neonatal diseases. A great majority of the participants at the Granada GBS Workshop have already agreed to involve their institution in such surveillance.
- All the European participants and invited North American speakers were really pleased by such an interesting and fruitful meeting. Unanimously, everybody expressed the wish to have a second enlarged European GBS workshop within the next two years.
- To organize either this second workshop or a European surveillance, C.McCartney (UK), G.Orefici (Italy) and P.Melin (Belgium) are very interested to involve themselves.

If ESCMID agrees, even if we are not ready to prepare a consensus paper, proceedings of the workshop could be published in a supplement of the "Clinical Microbiology and Infection". Most of the speakers have already accepted to write a paper of their presentation if requested.

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Stray-Pedersen,

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SESSION I Chairperson: Dr JC Santiago. Obstetrics & Gynaecology. Hosp. Virgen Nieves. Granada. Spain

Introductory remarks. Dr L Cabero, President Spanish Soc. Obstetrics & Gynaecology. Univ. Hosp. Vall d'Hebron. Barcelona

GBS neonatal disease, overview of the burden and the challenge of diagnosing neonatal bacterial sepsis. Dr S Salcedo and Dr J Vinzo. Neonatology. Univ. Hosp. Vall d'Hebron

Analysing prevention strategies. Dr WE. Benitz. Depart. Pediatrics, Stanford Univ. School Medicine, CA. USA

The European situation. The UK GBS Surveillance. Dr P Heath. St George's Hosp. Medical School. London. UK

France. Dr L Mereghetti. Microbiol. Univ. Tours, France

Italy. Dr G Orefici. Istit. Superiore Sanità. Roma. Italy

Austria and Germany. Dr K Schuchter. Ludwig Boltzman Inst. Clinical Obstetrics & Gynecology. Donauespital. Vienna, Austria

The UK practice. The obstetrician's opinion. Dr R Hughes, Royal Infirmary. Edinburgh. UK

Assessing the severity of the problem: "The Castrillo Group". Dr J Lopez Sastre. Neonatology. Oviedo and Dr M Sanchez Luna. Neonatology Univ. Hosp. Gregorio Marañón. Madrid

Questions

SESSION II Chairpersons: Dr J Quero. and Dr J Perez Rodriguez. Neonatology. Univ. Hosp. La Paz. Madrid

GBS in the antenatal clinic and in the delivery room: a matter of systematic attitude. Dr JM Foidart. President Belgian Royal Soc. Gynecology & Obstetrics. Univ. Hosp. Liège. Belgium

The microbiologist's perspective. Dr M de la Rosa. Microbiology. Univ. Hosp. Virgen Nieves. Granada

The CDC guidelines and their impact. Dr S Schrag, CDC. Atlanta. USA

GBS screening in US, current microbiological practice. Dr P Della-Latta. Microbiology. Columbia Presbyterian Medical Center. New York. USA

The Spanish Guidelines and experience and the situation in Portugal. Dr A Andreu, Microbiol. Univ. Hosp. Vall d'Hebron and Dr F Exposto. Inst. Higiene e Medicina Tropical. Lisbon. Portugal

Debate & Questions

SESSION III Chairpersons: Dr M de la Rosa and Dr E J Perea. Medical Microbiology. Univ. Sevilla

The Canadian Experience. Dr D Davies, Dep. Microbiology & Infectious Disease, Pediatrics & Community Health, Alberta Children's Hosp. Calgary Univ. Canada

The threat of resistant *E. coli*, myth or reality. Dr F Omeñaca and Dr A Alarcon. Neonatology. Univ. Hosp. La Paz

GBS neonatal disease prevention. Screening-based vs risk-based approaches. Dr G Gopal Rao. Microbiology. Lewisham Hosp. London. UK

Prevention of GBS transmission in labour: the topical approach. Dr GC di Renzo. Perinatal & Reproductive Medicine. Univ. Perugia and Dr F Facchinetti. Univ. Modena. Italy

How to manage a neonate born to a mother with risk factors for GBS disease. Dr WE Benitz

Special problems: Incomplete prophylaxis, caesarean delivery, allergies. Dr D Davies

Debate & Questions

SESSION IV Chairperson: Dr P Melin, Medical Microbiology. Univ. Hosp. Liege, Belgium

Round table and Interactive session

Summing up. Dr P Melin

Concluding remarks: Is a European opinion worthwhile and possible? Dr L Cabero